REMARKS

In a Final Office Action dated October 31, 2006 the Examiner in charge of this case rejected the claims of this application for a variety of reasons. Claims 1-11 are currently pending in the application; Claims 4-8 are withdrawn from consideration as being directed to a non-elected invention; Claims 1-3 and 9-11 are rejected under 35 U.S.C. §112, 1st ¶. Applicants respond by submitting the amendments and comments set forth hereinbelow. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

Specification Amendments

The specification is amended to correct additional clerical errors due to an inadvertent sequence misnumbering in the amino acid positions (see Table 1 at page 4, para. [00018] of the specification). Applicants believe that no new matter is added because basis for the amendment is found in the sequence comparison of Figure 2. Moreover, applicants believe that one skilled in the art would have recognized the existence of the error and the appropriate correction.

Claim Amendments

Claims 1and 3 are amended to affirmatively recite the difference in the deduced sequence relative to SEQ ID NO:4 is a threonine to a isoleucine substitution at amino acid position 52 of the SorCS1 amino acid sequence. Claim 2 is amended o affirmatively recite the difference in the determined cDNA sequence relative to SEQ ID NO:3 is a cytosine to a thymine substitution at nucleotide position 172 of the SorCS1 cDNA sequence. New Claim 12 includes the preamble of Claim 3 and the cDNA sequence limitations of Claim 2. Accordingly, Claims 9-11 are canceled to avoid duplication. No new matter is added. Support for these amendments is found, for example, at page 3-5 of the specification. In view of these amendments, applicants respectfully request reconsideration and withdrawal of the rejections issued in this case.

New Matter Objection

The Examiner asserts the amino acid clarification made in Table 1, at pg. 4 of the Specification (i.e., from "50" to "52" for the Thr/Ile, B6/BTBR, respectively) is not supported by the original disclosure. Applicants respectfully disagree.

Applicants submit the amendment made to correct the inadvertent misnumbering (an obvious error) does not constitute new matter because it is believed that one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction (MPEP 2163(I)(B)). The instant specification provides adequate guidance to demonstrate that the correct amino acid position is 52 and this position is conserved among both human and mouse SorCS1. Applicants acknowledge the Examiner's identification of a threonine also conserved across species at amino acid position 68. However, a skilled artisan would readily recognize that none of the nucleotide sequences in that vicinity correlate with the nucleotides surrounding and at position 172 of the SorCS1 cDNA sequence.

Moreover, one of ordinary skill in the art would recognize the appropriate amino acid position is "52" not "50". To support the notion that the sequence correction was easily recognized by those in the field, the mouse SorCS1 cDNA and protein sequences are recited below. These sequences illustrate the 17 nucleotide 5'UTR (underlined for emphasis) as it relates to the location of the nucleotide (position 172) and corresponding amino acid (position 52) mutation.

B6 sequence

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ttctctacgctccagagatgggaaaagttggcgctggagacggctcctcggccgggctgagc
                    M  G  K  V  G  A  G  D  G  S  S  A  G  L  S
gcgctccttgcaggagcggggcttctgatgctcttagcccccggcgtctgcagcagcctc
 A  L  L  A  G  A  G  L  L  M  L  L  A  P  G  V  C  S  S  L
tcttgctgccctccgcagcaccctagctcgaccccacgccggacccttacc ...
 S  C  C  P  P  Q  H  P  S  S  T  P  R  R  T  L  T
                                                  52
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BTBR sequence has a c to t change at 172 bp which changes the amino acid residue at position 52.

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ttctctacgctccagagatgggaaaagttggcgctggagacggctcctcggccgggctgagc
                    M  G  K  V  G  A  G  D  G  S  S  A  G  L  S
gcgctccttgcaggagcggggcttctgatgctcttagcccccggcgtctgcagcagcctc
 A  L  L  A  G  A  G  L  L  M  L  L  A  P  G  V  C  S  S  L
tcttgctgccctccgcagcaccctagctcgaccccacgccggacccttatc ...
 S  C  C  P  P  Q  H  P  S  S  T  P  R  R  T  L  I
                                                  52
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As further support that the correction of the amino acid position in Table 1 is not new matter, applicants submit the sequences in Table 1 are mutations found in the mouse SorCS1 sequence. The SorCS1 nucleotide position in Table 1, therefore, correspond to the SorCS1

mouse cDNA sequence. If this cDNA is translated with the mutation of c to t at 172, this results in a thr to ile change at amino acid 52 of the mouse sequence. The codons are acc to atc. It would be obvious to those in the field that translation of the mouse cDNA sequence places nucleotide (nt) 172 in codon 52 not 50.

Next, as the 5' untranslated sequence in the mouse cDNA is 17 nt instead of 8 nt found in the human cDNA sequence given. The difference is 9bp (3 codons). That is, the human sequence is nine nucleotides shorter than the mouse sequence. So, nt 172 in the mouse corresponds to nt 163 (172 - 9) in the human. As seen in the human cDNA sequence given in the patent, this is an acc codon (as in the B6 mouse) corresponding to Thr at amino acid 52. Accordingly, given that mouse cDNA positions in Table 1 were based on the mouse cDNA sequence (publicly available), applicants submit that one skilled in the art would have recognized the existence of the inadvertent misnumbering and the appropriate correction.

Claim Rejections - 35 USC §112

Claims 1-3 and 9-11 stand rejected under 35 USC §112, 1st paragraph as lacking enablement. Applicants do not agree with the rejection. However, to facilitate prosecution on the merits, Claims 1-3 are amended and Claims 9-11 are canceled herein. It is believed these amendments overcome the §112 issues cited in the Action.

In addition, applicants reiterate the specification sets forth at page 5, paragraph [00019] that the genomic and cDNA sequences of both mouse and human SorCS1 were known to those of ordinary skill in the art at the time of filing. The specification incorporates by reference the human SorCS1 cDNA sequence (GenBank Accession No. NM_052918) and amino acid sequence (GenBank Accession No. NP_443150). The specification also discloses that the mouse SorCS1b (mSorCS1b) and human SorCs1 (hSorcs1, the "b" isoform) in Figure 2 are highly homologous (i.e., 93% sequence identity). This degree of identity between the mouse and human SorCS1 coding region is sufficient to soundly predict that applicants' genetic evidence from the congenic mouse model is predictive of the same genetic phenomenon (i.e., susceptibility to T2D) in humans.

The Examiner continues to indicate "[t]he specification asserts at page 3 that the SorCS1 gene in mice is 'directly analogous' to the human gene, however this statement is unclear." The

Examiner goes on to point out a discrepancy in the amino acid sequence positions of residues 1139 and 1149.

Applicants submit that the phrase "directly analogous" is intended to mean that the mouse and human SorCS1 genes are similar in structure and function. This correlation between mouse and human SorCS1 is made sufficiently clear in the specification, which provides, for example:

> "that the sequences are highly homologous, in fact have a sequence identity of 93%. It is this degree of identity that provides the rational for the prediction that the genetic evidence from the congenic mouse model presented here does, in fact, predict the same genetic phenomenon in humans." (See Specification, pg. 5, underlining for emphasis)

Thus, it is believed that the correlation between the SorCS1 gene in mice and the human gene is abundantly clear to those of ordinary skill in the art.

As to the discrepancy in the amino acid sequence positions of residues 1139 and 1149, applicants have corrected this inadvertent clerical correct herein above. This correction is made not for reasons related to patentability but to ensure that the data in the specification is scientifically accurate. This correction of an inadvertent error is not believed to affect the scope of the claims at issue. It is believed that no new matter is added. Thus, applicants respectfully request reconsideration and withdrawal of these rejections.

Furthermore, the Examiner continues to assert that although the specification discloses at paragraph [00033] the SorCS1 protein is active in determining islet mass, insulin secretion in pancreatic beta cells or insulin degradation in the kidney or liver, (1) SorCS1 function is not taught, nor is (2) how the mutations disclosed alter the function of the SorCS1 nucleic acid or protein such that the change provides an increase in susceptibility to type 2 diabetes.

In response, applicants submit the SorCS1 protein is active in determining the levels of islet mass, insulin secretion in pancreatic beta cells or insulin degradation in the kidney or liver and will affect plasma insulin levels, which are altered in the congenic mice disclosed. Specifically, it is believed the reduced or altered insulin levels in the congenic mice are a result of decreased insulin secretion *in vivo*, which is associated with disrupted islet morphology.

Furthermore, it is noted the cellular function of SorCS1 is still unknown, however, it is known to bind platelet derived growth factor-BB. This growth factor is required for the recruitment of pericytes or their precursors to vascular endothelial cells, where they stabilize the microvasculature and have a key role in blood vessel development. Maintenance of proper islet

vasculature is important for both insulin secretion and islet survival and thus may be of particular relevance to the mammalian phenotype disclosed in the instant application.

Applicants wish to reiterate the importance of applicants' discovery for the Examiner. Applicants were the first to establish that the SorCS1 gene is one of the genetic factors responsible for T2D and linked severe T2D to a 7MB segment of mouse chromosome 19. Applicants established that a predictable correlation exists between a structural alteration in the SorCS1 protein (mouse and human) and susceptibility for developing T2D in humans. To establish this correlation, applicants mapped 2 loci associated with diabetes susceptibility in mice. One locus on chromosome 16 was associated with a less severe form of diabetes and the second locus on chromosome 19 was associated with a more severe form of T2D. Applicants discovered that mice having the severe form inherited a 7 Mb segment of chromosome 19 from a parent and exhibited very high levels of plasma glucose, averaging 120 mg/dl higher. Applicants thus characterized the genes and sequences in the 7 Mb region to identify a genetic element responsible for the differential in susceptibility to diabetes.

Applicants discovered that the alleles of all genes carried in the region by the more severely and less severely diabetic mice were the same except for the allele of the SorCS1 gene. Fig. 1 illustrates a genetic map of the genetic elements found in the 7 Mb region associated with the genetic difference. Applicants identified the region between map units 55 and 48 as carrying the genetic difference. Applicants determined that the more severely diabetic mice have an allele of the SorCS1 gene that differs at three amino acids from the allele of that same protein in mice with the less severe form of T2D (see Table 1). Applicants disclose that the threonine residue at position 52 in mouse and human SorCS1 (see sequence comparison of Fig. 2) is an evolutionarily conserved residue. It is also disclosed that a mutation of the threonine residue in that region is an indicator for a subject's susceptibility for developing T2D.

Applicants discovered that the difference in susceptibility to diabetes resolved down to differences in the alleles of the gene for SorCS1. Since the same correlation that exists in mice also exists in humans, and since the corresponding homologous SorCS1 gene having a conserved threonine at amino acid residue 52 is found in both mice and humans, the same susceptibility to developing T2D is found in humans and in mouse. (See page 3, [00015] of the specification). Thus, a predictive association between mouse and human SorCS1 protein and susceptibility to developing T2D is established in the present application.

It is further noted that, among the genes analyzed in mice, SorCS1 is the only gene for which applicants detected amino acid substitutions and expression level differences. In fact, applicants believe that these expression differences cause the increased diabetes risk (i.e., increased expression = increased risk of developing T2D). Through this analysis applicants identified the variation within the SorCS1 gene that underlied the T2D phenotype. Applicants believe the SorCS1 gene is at least one of the sources of genetic susceptibility to T2D and allelic differences in this gene are alone sufficient to explain some of the genetic susceptibility to the disease. Based on this notion, it was predicted that human genetic tests could be performed to determine if a subject is genetically susceptible to T2D due to his or her SorCS1 gene allele. Thus, it is believed that applicants have satisfied all of the patentability requirements.

Claims 1-3 and 9-11 stand rejected under 35 USC §112, 1st paragraph as lacking written description. Applicants do not agree with the rejection. However, to facilitate prosecution on the merits, Claims 1-3 are amended and Claims 9-11 are cancelled herein.

Accordingly, applicants respectfully request that in view of these claim amendments and comments, the rejection be reconsidered, withdrawn and that a timely Notice of Allowance be issued in this case.

A Petition for Extension of Time and a Request for Continuing Examination (RCE) accompany this response so the response will be deemed timely filed. Please charge these fees to Deposit Account No. 17-0055. No other fees are believed due. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17 0055.

Respectfully submitted,

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